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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

July 21, 2000

Docket Number 00D-0835

Gentlemen:

Enclosed are the comments of the ALEX Pharmaceutical Co. on the "Guidance for Industry, Conjugated Estrogens, USP--LC-MS Method for Both Qualitative Chemical Characterization and Documentation of Qualitative Pharmaceutical Equivalence" which was published in the Federal Register of March 9, 2000. The closing date for comments was June 8, 2000, however, we are submitting these comments with the hope that they will be considered by the Agency. We are appreciative of the opportunity to comment. The undersigned is a consultant for ALEX Pharmaceutical.

We find four problems with the draft guidance that should be corrected before this guidance is finalized. They are:

1. The guidance does not list the delta 8-9 DHES compound as one of the compounds to be determined along with estrone-3-sulfate, equilin-3-sulfate and sodium 17-dihydroequilin-3-sulfate. Dr. Janet Woodcock, Director of CDER, FDA, mentioned the important clinical contribution of this compound in her memorandum on natural conjugated estrogens dated May 5, 1997.
2. The method does not appear to analyze for free steroids since it uses a water extraction method. Thus, it is possible that the method could analyze degraded samples of conjugated estrogen without the analyst being aware of it since the degradation products are free steroids.
3. The piperazine equilin-3-sulfate used as a standard is not commercially available as far as we can determine. Some readily available standard is needed.
4. The draft guidance in which the Agency will give detailed recommendations on how to determine the qualitative LC-MS data and acceptance criteria for documentation of qualitative pharmaceutical equivalence needs to be finalized at the same time as the present draft guidance and, as yet, it is not out for comment. Without this additional information it is impossible to fully evaluate the performance, precision, and reproducibility of the analytical method described.

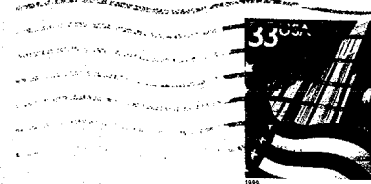
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